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PATENT SPECIFICATION

746,015

Date of Application and filing Complete Specification: June 24, 1952.
No. 27387/54.
Application made in United States of America on Oct. 1, 1951.
(Divided out of No. 745,900).
Complete Specification Published: March 7, 1956.

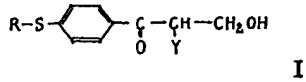
Index at acceptance:—**Class 2(3)**, C1A(13:15), C1B4, C1C(3:5:8), C1C11(D:F:J), C1D, C2D(3:19), C3C5.

COMPLETE SPECIFICATION

Acylamino Phenone Compounds and method for preparing same

We, STERLING DRUG INC., a corporation organised under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which is is to be performed, to be particularly described in and by the following statement:—

This invention relates to new chemical compounds and the preparation thereof, said compounds being useful as intermediates for the production of other chemical compounds. This application is a divisional of Application 15864/52 (Serial No. 745,900) and the use of the compounds of the present invention as intermediates is disclosed in that application. More particularly, this invention relates to new compounds having the formula

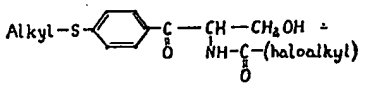


I

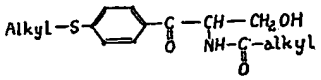
where R is a hydrocarbon radical having 1—7 carbon atoms, and Y is an aliphatic carboxylic acylamino radical. The hydrocarbon radical R includes aliphatic, cycloaliphatic, aryl, and benzyl radicals having 1—7 carbon atoms and represents, for example: branched and unbranched alkyl radicals, such as methyl, ethyl, n-propyl, n-butyl, isobutyl, n-heptyl, isoamyl, alkenyl radicals, such as allyl, methallyl; cycloalkyl radicals, such as cyclohexyl, cyclopentyl; benzyl; phenyl; and ortho-, meta-, and para-tolyl radicals. The acylamino radicals represented by Y include both saturated and unsaturated aliphatic carboxylic acylamino radicals wherein the aliphatic carboxylic acyl group can be considered as being derived from an aliphatic carboxylic acid. Thus, for example, Y can be alkanoylamino, haloalkanoylamino, nitroalkanoylamino or alkylmercaptoalkanoylamino. We particularly prefer acyclic lower aliphatic carboxylic acylamino radicals containing 1—4 carbon atoms. This preferred group of acyl radicals includes, for example, acetylamino, dichloroacetylamino, dibromoacetylaminobromoacetylamino, beta-chloropropionylamino, difluoroacetylamino, alpha-chloropropionylamino, trichloroacetylamino, nitroacetylamino, methylmercaptoacetylamino, methylsulfonylacetylamino, ethylmercaptoacetylaminobutylrylamino, alpha-methylpropionylamino, alpha,alpha-dichloropropionylamino, iodoacetylamino, cyanoacetylamino, methoxyacetylamino, acrylylamino, and alpha-hydroxypropionylamino.

The following groups of compounds embraced by the generic formula hereinabove are illustrative of the products provided by the invention:

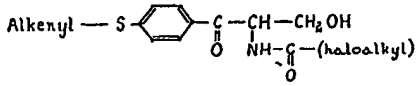
alpha-Haloalkanoylamino-beta-hydroxy-4-alkylmercaptopropiophenones, having the formula



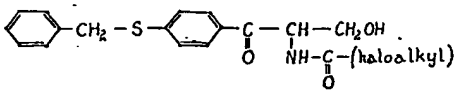
alpha-Alkanoylamino-beta-hydroxy-4-alkylmercaptopropiophenones, having the formula



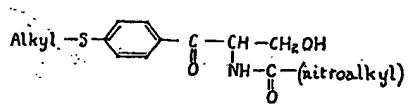
alpha-Haloalkanoylamino-beta-hydroxy-4-alkenylmercaptopropiophenones, having the formula



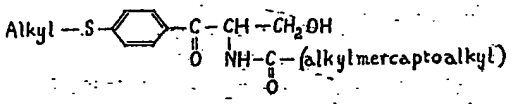
alpha-Haloalkanoylamino-beta-hydroxy-4-benzylmercaptopropiophenones, having the formula



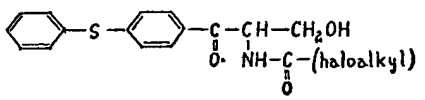
alpha - Nitroalkanoylamino - beta -hydroxy-4 - alkylmercaptopropiophenones, having the formula



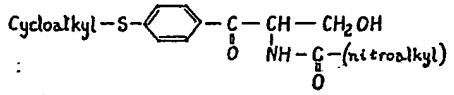
alpha - Alkylmercaptoalkanoylamino - beta-hydroxy - 4 - alkylmercaptopropiophenones, having the formula



alpha - Haloalkanoylamino - beta - hydroxy-4 - phenylmercaptopropiophenones, having the formula

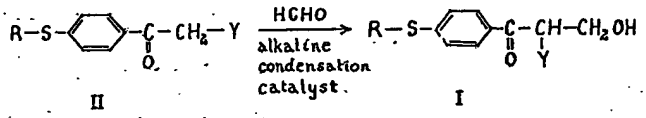


alpha - Nitroalkanoylamino - beta - hydroxy-4 - cycloalkylmercaptopropiophenones, having the formula



In accordance with the invention, the new alpha-aliphatic carboxylic acylamino-beta-hydroxy - 4 - hydrocarbonylmercaptopropiophenones are prepared by hydroxymethylating a compound of the formula II to produce a compound of the formula I.

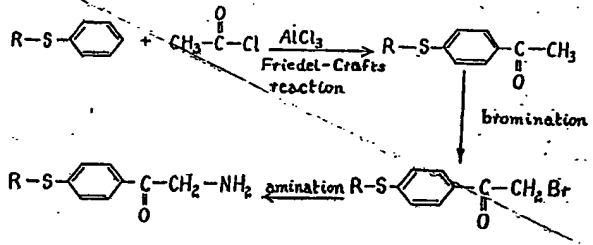
In the preferred embodiment of the invention an alpha-(aliphatic carboxylic acylamino)-4 - hydrocarbonyl - mercaptoacetophenone (II) is treated with formaldehyde in the presence of sodium bicarbonate, thereby producing an alpha-(aliphatic carboxylic acylamino)-beta-hydroxy - 4 - hydrocarbonylmercaptopropiophenone (I). The reaction involved in this process is represented by the following equation:



In our process, formaldehyde in the form of a gas, aqueous or alcoholic solution or paraformaldehyde is interacted with the acylaminophenone (III). This reaction is most conviently carried out at 20-50° C., but temperatures considerably above and below this temperature range, for example in the range 0-70° C., also afford satisfactory results. The amount of catalyst employed is not critical, but for best results we prefer to employ the smallest amount of catalyst sufficient to bring about a reasonably rapid reaction. In general, about 0.01-0.10 mole of the catalyst is sufficient to afford satisfactory results.

The alpha - (aliphatic carboxylic acylamino)-4 - hydrocarbonylmercaptoacetophenones (II) employed as starting materials in our process are readily obtained, for example, by treating the appropriate alpha-amino-4-hydrocarbonylmercaptoacetophenones (IV) in conventional fashion with an aliphatic carboxylic acylating agent such as an acyl halide or anhydride. The acylation can be carried out, for example, by heating the acylating agent and the amine (IV) in an anhydrous organic solvent or in an alkaline aqueous solution. The temperature of the reaction can be varied within rather wide limits, but a range of 0-100° C. is generally satisfactory.

The alpha - amino - 4 - (hydrocarbonylmercapto)acetophenones (IV) are themselves conveniently prepared from hydrocarbonyl phenyl sulphides in accordance with the following sequence of reactions:



IV

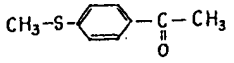
The invention is illustrated by the following examples without, however, being limited thereto.

EXAMPLE I

A. ALPHA - AMINO - 4 - METHYLMERCAPTOACETOPHENONE HYDROCHLORIDE.

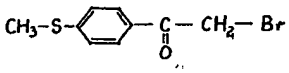
110 g. of thiophenol was added with stirring to a mixture of 90 ml. of 35% aqueous sodium hydroxide solution and 400 ml. of water in a 2-litre, 3-neck flask. To the resulting mixture, there was added 139 g. of dimethyl sulphate from a dropping funnel at such a rate that the temperature of the reaction mixture did not rise above 60° C. while applying external ice cooling to the reaction vessel. The addition of the dimethyl sulphate required about five to ten minutes. After the addition of dimethyl sulphate was completed, stirring of the reaction mixture was continued for about one hour, and then the mixture was cooled. The thioanisole which separated from the mixture was dissolved in about 400 ml. of chloroform. The chloroform solution was separated, washed with 100 ml. of dilute aqueous sodium hydroxide solution, and dried over anhydrous calcium sulphate. (In other experiments, isolation of the product from the chloroform solution resulted in recovery of thioanisole in a yield of 90-95% of the theoretical based on the quantity of thiophenol employed).

The chloroform solution of thioanisole was filtered free from the calcium sulphate directly into a 2-litre, 3-neck flask fitted with a stirrer, thermometer, dropping funnel and outlet tube (for escape of hydrogen chloride gas) protected by a drying tube. Sufficient anhydrous chloroform was added to the filtrate to bring the volume up to about 800 ml. and the solution was cooled by means of an ice-methanol bath. 165 g. of aluminium chloride was then added rapidly to the chloroform solution, while keeping the temperature of the solution below 10° C. 106 g. of acetyl chloride was added to the solution by means of a dropping funnel while still maintaining the temperature of the reaction mixture below 10° C. As the addition of the acetyl chloride proceeded, a yellow solid gradually separated from the mixture. (In some instances, it was found desirable to add an additional quantity of dry chloroform to the reaction mixture in order to facilitate stirring). When the addition of the acetyl chloride was completed, the cooling bath was removed and the reaction mixture was allowed to warm to 20° C. while continuing vigorous stirring. The thick reaction mixture was then decomposed by pouring it into a litre of ice and water containing 30-50 ml. of concentrated hydrochloric acid with vigorous stirring to ensure complete decomposition of the complex. The chloroform layer, which contained 4-methylmercaptoacetophenone, having the formula



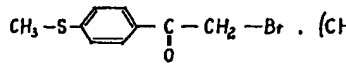
was separated and employed directly in the subsequent step. (In other experiments, by evaporation of the chloroform solution there was obtained in 96-98% yield 4-methylmercaptoacetophenone in a high degree of purity).

The chloroform solution of 4-methylmercaptoacetophenone was placed in a 3-litre, 3-neck flask fitted with a stirrer, a dropping funnel, and an outlet tube for escape of hydrogen bromide gas. The volume of the chloroform solution was brought up to about 1600 ml. by addition of chloroform. About 40 g. of bromine was added to the solution and the mixture was allowed to stand until the reaction was initiated, as evidenced by evolution of hydrogen bromide. Stirring of the mixture was then begun and a further quantity of 120 g. of bromine was added during a period of three to five minutes. The reaction mixture was then placed under reduced pressure by application of a water aspirator in order to remove the major portion of the hydrogen bromide. The temperature of the solution, which contained alpha-bromo-4-methylmercaptoacetophenone, having the formula



gradually fell, due to evaporation, to about 10-15° C. (A sample of this bromo ketone, isolated in another experiment, was obtained in the form of small white leaflets, which melted at 65.5-66.5° C., after recrystallization from methanol).

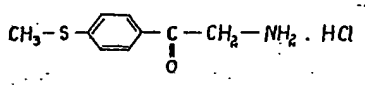
To the cold chloroform solution of alpha-bromomercaptoacetophenone, there was added 140 g. of hexamethylenetetramine. The temperature of the mixture rose gradually to about 30-35° C., and a white solid separated from the mixture. The mixture was stirred for about two hours and then the solid was collected on a filter and washed with chloroform. The product thus obtained consisted of alpha - bromo - 4 - methylmercaptoaceto phenone-hexamethylenetetramine adduct, having the formula



and melting at approximately 140° C. with decomposition.

The alpha-bromo-4-methylmercaptoacetophenone - hexamethylenetetramine adduct obtained in the preceding step was placed in a 3-litre flask with 750 ml. of ethanol and 375

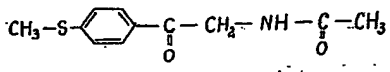
ml. of concentrated hydrochloric acid. As the mixture was stirred, producing a slurry, the solid gradually went into solution. The reaction product subsequently began to separate from the solution. The reaction mixture was then cooled to 10° C., filtered, and the filter cake was washed with 100 ml. of cold ethanol. The damp filter cake was then slurried for a few minutes at 40-50° C. with 600 ml. of water containing 25 ml. of concentrated hydrochloric acid. After cooling the slurry to 5—10° C., the white solid was collected on a filter, washed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid, and dried. There was thus obtained 135-141 g. of alpha-amino - 4 - methylmercaptoacetophenone hydrochloride, having the formula



A sample of this product when recrystallized from water formed large white leaflets which melted at 234.5-235° C. (dec.).

B. ALPHA-ACETYLAMINO-4-METHYLMERCAPTOACETOPHENONE.

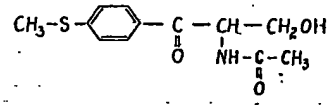
A slurry of 11 g. of alpha-amino-4-methylmercaptoacetophenone hydrochloride in 50 ml. of water containing 100 g. of ice was stirred vigorously and to the slurry there were added in one portion 10 ml. of acetic anhydride followed by a solution of 14.5 g. of sodium acetate trihydrate in 60 ml. of water. The temperature of the reaction mixture, which did not rise during addition of the acetic anhydride and sodium acetate, was allowed to rise to room temperature (about 25° C.) and stirring was continued for an additional two hours. Sufficient concentrated hydrochloric acid was then added to make the reaction mixture acid to Congo Red paper (to dissolve any unreacted aminoketone), and the white solid in the mixture was then collected on a filter. This solid was washed with 30 ml. of water and dried. There was thus obtained 10 g. of alpha - acetylamino - 4 - methylmercaptoacetophenone, having the formula



which melted at 133.2-134.6° C., after recrystallization from acetone in the form of broad white needles.

C. ALPA - ACETYLAMINO-BETA - HYDROXY - 4-METHYLMERCAPTOPROPIOPHENONE.

A mixture of 15 g. of alpha-acetylamino-4-methylmercaptoacetophenone, 70 ml. of ethanol, 25 ml. of water, 10 ml. of formalin (37% aqueous solution of formaldehyde), and a solution of 0.3 g. of sodium bicarbonate in 10 ml. of water was stirred at 35° C., for two hours. The original thick slurry gradually thinned out and after about ten minutes the reaction mixture was a pale yellow solution. At the end of the two-hour period, the solution was refrigerated for about ten hours. The crystalline solid which separated from the cooled solution was collected on a filter and washed with 20 ml. of water. There was thus obtained 10.5 g. of alpha-acetylamino-beta-hydroxy-4-methylmercaptopropiophenone, having the formula

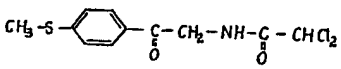


This product was purified by recrystallization from ethyl acetate to yield white fluffy needles which melted at 125.6-127.8° C.

EXAMPLE 2

A. ALPHA - DICHLOROACETYLAMINO - 4-METHYLMERCAPTOACETOPHENONE.

217.7 g. of alpha-amino-4-methylmercaptoacetophenone hydrochloride obtained as described in part A of Example 1 was mixed with 4.5 litres of anhydrous benzene at 27° C. 166 g. of dichloroacetyl chloride was added in one portion to the mixture, and the resulting mixture was refluxed and stirred for fifteen to eighteen hours. After this period most of the solid had gone into solution. The reaction mixture was filtered hot through a preheated funnel and the filtrate was allowed to cool. The solid which separated from solution was collected on a filter, washed with benzene, and dried. There was thus obtained 230 g. of alpha - dichloroacetylamino - 4 - methylmercaptoacetophenone having the formula

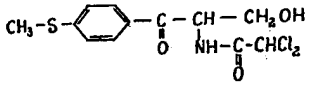


Recrystallization of this product from acetone yielded white needles which melted at 151.7-152.9° C.

B. ALPA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - METHYLMERCAPTOPROPIOPHENONE.

292.2 g. of alpha-dichloroacetylamino-4-methylmercaptoacetophenone was slurried with 14.5 litres of ethanol at 40° C. 15 g. of sodium bicarbonate and 150 ml. of formalin (37% aqueous solution of formaldehyde) were added to the mixture and stirring was continued while maintaining the temperature of the solution at 40-50° C. until all of the alpha-dichloroacetylamino - 4 - mercaptoacetophenone had gone into solution. This required about eight hours. The suspended sodium bicarbonate was then removed by filtration and the volume of the filtrate was reduced to 2-2.5 litres by evaporation of ethanol from the solu-

tion under reduced pressure. The residual solution, which had an orange colour, was refrigerated for about ten hours. The solid which separated from the solution was collected on a filter. There was thus obtained 232 g. of alpha-dichloroacetylamino-beta-hydroxy-4-methylmercaptopropiophenone having the formula

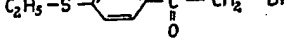


Recrystallization of this product from ethylene chloride yielded tiny white leaflets which melted at 147.7-148.5° C.

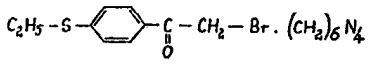
EXAMPLE 3

A. ALPHA - AMINO - 4 - ETHYLMERCAPTOACETOPHENONE HYDROCHLORIDE.

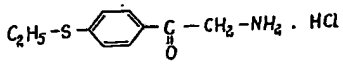
337 g. of ethyl sulphate was added from a dropping funnel to a stirred solution of 200 g. of thiophenol in 800 ml. of 10% aqueous sodium hydroxide. The reaction mixture was then stirred for two hours. During this period the temperature of the mixture gradually rose to 65° C. and then decreased to room temperature (about 25° C.) and the desired reaction product, ethyl phenyl sulphide, separated from the mixture as an oil. This oil was extracted from the mixture with 800 ml. of chloroform. The chloroform solution of ethyl phenyl sulphide thus obtained was dried for several hours over anhydrous calcium sulphate. The dry solution was then placed in a 3-litre, 3-neck flask fitted with a stirrer, thermometer, and drying tube. The solution was stirred and cooled to −10° C. and 175 ml. of acetyl chloride was added. 300 g. of anhydrous aluminium chloride was then added portionwise while keeping the temperature of the reaction mixture at 5-15° C. After the addition of the aluminium chloride was completed, the reaction mixture was allowed to warm to 20° C. and was poured into about 2 kg. of ice. The chloroform layer, which contained the desired 4-ethylmercaptoacetophenone, was separated from the mixture and placed in a 5-litre, 3-neck flask fitted with a stirrer and dropping funnel. To the stirred solution there was added 75 g. of bromine. After the reaction was initiated, as shown by the evolution of hydrogen bromide, an additional 225 g. of bromine was added as rapidly as was practical. The hydrogen bromide evolved from the mixture was removed by applying reduced pressure to the stirred solution, which contained alpha-bromo-4-ethylmercaptoacetophenone, having the formula



(A sample of the bromoketone isolated in another experiment melted at 74.4-75.4° C. after recrystallization from petroleum ether followed by recrystallization from methanol.) To the residue thus obtained, there was added 256 g. of hexamethylenetetramine, and the mixture was stirred for two hours. The solid yellowish alpha-bromo-4-ethylmercaptoacetophenone-hexamethylenetetramine adduct having the formula



was collected on a filter, washed with chloroform and sucked partially dry on the filter. The adduct was mixed with 760 ml. of concentrated hydrochloric acid and 1540 ml. of ethanol, and the mixture was stirred for about six hours. The resulting suspension was cooled to 5° C., and was filtered and washed with about 200 ml. of ethanol. The solid was then slurried with one litre of warm water containing 20 ml. of concentrated hydrochloric acid. This suspension was cooled to 5° C. and then filtered. The collected solid was washed with about 300 ml. of ice water and dried. There was thus obtained 211 g. of alpha-amino-4-ethylmercaptoacetophenone hydrochloride, having the formula



This product melted at 186.5° C. (dec.) after recrystallization from water which had been made slightly acid with dilute hydrochloric acid.

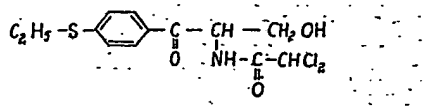
B. ALPHA - DICHLOROACETYLAMINO - 4-ETHYLMERCAPTOACETOPHENONE.

A mixture of 200 g. of alpha-amino-4-ethylmercaptoacetophenone hydrochloride and 4.5 litres of benzene was placed in a 12-litre, 3-neck flask fitted with a stirrer and a reflux condenser with water trap. The benzene was distilled slowly until no more water collected in the water trap. 147 g. of dichloroacetyl chloride was added to the mixture in a single portion and the resulting mixture was refluxed for fifteen hours. The evolution of hydrogen chloride had practically ceased at the end of this period and all of the solid in the mixture had dissolved. The hot solution was filtered. On cooling, there separated from the filtrate 139 g. of white solid which consisted of alpha-dichloroacetylamino - 4 - ethylmercaptoacetophenone having the formula

This product melted at 127.6-128.8° C. after recrystallization from ethylene chloride. An additional 66 g. of the product was recovered by evaporation of the filtrate to a volume of 600 ml., cooling, and collecting the solid which separated from solution.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - ETHYLMERCAPTOPROPIOPHENONE.

A mixture of 200 g. of alpha-dichloroacetylamino-4-ethylmercaptoacetophenone, 100 ml. of formalin (37% aqueous solution of formaldehyde), 1600 ml. of ethanol, and 10 g. of sodium bicarbonate was stirred at 40-50° C., for ten hours. The mixture was allowed to stand at room temperature for about fifteen hours and was then cooled to 10° C. The solid which separated from the cooled solution was collected on a filter, was washed with 150 ml. of ethanol, and dried. There was thus obtained 204 g. of alpha-dichloroacetylamino-beta-hydroxy-4-ethylmercaptopropiophenone, having the formula

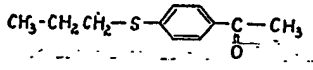


which melted at 150-152° C. When recrystallized in the form of small white leaflets of ethylene chloride, the pure compound melted at 153.2-154.3° C.

EXAMPLE 4

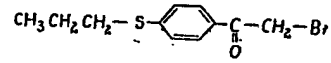
A. ALPHA - AMINO - 4 - N - PROPYLMERCAPTOACETOPHENONE HYDROCHLORIDE

A suspension of 226 g. of aluminium chloride in one litre of dry chloroform was placed in a 3-litre, 3-neck flask fitted with a stirrer, drying tube, dropping funnel and thermometer. The suspension was stirred and cooled to 5° C. with stirring and 145 g. of acetyl chloride was added. 235.5 g. of n-propyl phenyl sulphide was then added dropwise at 5° C. The reaction mixture was stirred for fifteen minutes after addition of the sulphide was completed, and was then poured into 1.5 kg. of ice containing 25 ml. of concentrated hydrochloric acid. The chloroform layer was separated from the mixture and the chloroform was removed from the solution by distillation. The residual oil was fractionally distilled, and the fraction boiling at 207° C. at 45-48 mm. of mercury was collected. There was thus obtained 253 g. of colourless oil which solidified upon standing. This product, which was 4-n-propylmercaptoacetophenone, having the formula



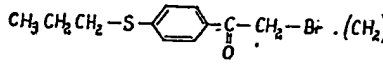
melted at 37.7-39.1° C.

208 g. of bromine was added to a solution of 254 g. of 4-n-propylmercaptoacetophenone in 2 litres of chloroform. After five or ten minutes, the evolution of hydrogen bromide from the reaction mixture had practically ceased, and the mixture was washed with 2 litres of 5% aqueous sodium bicarbonate solution containing ice. The chloroform layer was separated from the mixture and the chloroform was removed from the chloroform solution by distillation at reduced pressure. There was thus obtained as a residue 300 g. of alpha-bromo-4-n-propylmercaptoacetophenone having the formula



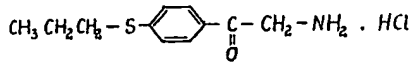
in the form of an orange coloured oil which was used directly in the next step of the process. Crystallization of a sample of this product from petroleum ether yielded a white solid which melted at approximately 43° C.

95 g. of hexamethylenetetramine was added with stirring to a solution of 176 g. of alpha-bromo - 4 - n - propylmercaptoacetophenone dissolved in 850 ml. of acetonitrile. The temperature of the reaction mixture rose from 28° C. to 42° C. and a pale yellow solid separated from solution. After stirring the mixture for two hours, the solid was collected on a filter, washed with two 150 ml. portions of acetonitrile, and with 300 ml. of water, and dried. There was thus obtained, as a pale yellow solid, 174 g. of alpha-bromo-4-n-propylmercaptoacetophenone - hexamethylenetetramine adduct having the formula



which melted at approximately 135° C. with decomposition.

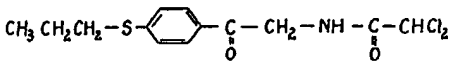
192 g. of alpha-bromo-4-n-propylmercaptoacetophenone-hexamethylenetetramine adduct was mixed with a solution of 90 ml. of concentrated hydrochloric acid and 225 ml. of methanol, and the mixture was stirred and refluxed for thirty minutes. Initially, the mixture became dark red in colour and after about ten minutes ammonium chloride separated from the solution. The ammonium chloride was removed by filtration, and the filtrate was cooled to −5° C. The solid which separated from the cooled solution was collected on a filter and dissolved in 125 ml. of hot water. The aqueous solution was cooled to 0° C. and the solid which separated from solution was collected on a filter. There was thus obtained 27 g. of alpha-amino-4-n-propylmercaptoacetophenone hydrochloride having the formula



which melted at approximately 155° C. with decomposition.

B. ALPHA - DICHLOROACETYLAMINO - 4 - N-PROPYLMERCAPTOACETOPHENONE.

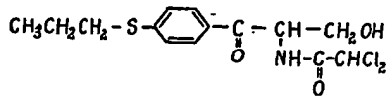
27 g. of alpha-amino-4-n-propylmercaptoacetophenone hydrochloride was added to 500 ml. of benzene and the resulting mixture was refluxed until no more water distilled off into a water separator. 41 g. of dichloroacetyl chloride was then added and the mixture was stirred and refluxed for thirty minutes. During this period all of the ketoamine dissolved. The resulting reaction mixture was concentrated under reduced pressure, and the residue thus obtained was refrigerated. The solid which separated from the cooled solution was collected on a filter, washed with 5 ml. of benzene, and dried. There was thus obtained 16.5 g. of alpha-dichloroacetylamino-4-n-propylmercaptoacetophenone, having the formula



which was recrystallized from benzene as a white solid which melted at 123.2-123.8° C.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - N - PROPYLMERCAPTOPROPIOPHENONE.

A mixture of 13 g. of alpha-dichloroacetylamino-4-n-propylmercaptoacetophenone, 100 ml. of ethanol, and 8 ml. of formalin (37% aqueous solution of formaldehyde) containing 0.8 g. of sodium bicarbonate dissolved therein, was stirred at 40-43° for four hours. The reaction mixture was then cooled and the solid which separated from the solution was collected on a filter. There was thus obtained 12.5 g. of alpha-dichloroacetylamino-beta-hydroxy-4-n-propylmercaptopropiophenone, having the formula

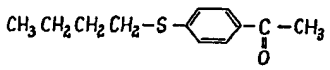


This product was recrystallized from ethylene chloride, thereby yielding 10 g. of the pure compound which melted at 133.4-136.8° C.

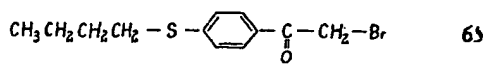
EXAMPLE 5

A. ALPHA - AMINO - 4 - N - BUTYLMERCAPTOACETOPHENONE.

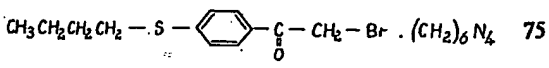
This compound was prepared in a manner analogous to that described in part A of Example 4 above for the preparation of the corresponding n-propylmercapto compound. 250 g. of n-butyl phenyl sulphide was treated with 133 g. of acetyl chloride in the presence of 220 g. of aluminium chloride. There was thus obtained 206 g. of 4-n-butylmercaptoacetophenone, having the formula



which boiled at 138-140° C. at 0.8 mm. and melted at 24-25° C. after crystallization from petroleum ether at 0° C. 110 g. of 4-n-butylmercaptoacetophenone dissolved in one litre of chloroform was treated with 80 g. of bromine to yield 168 g. of alpha-bromo-4-n-butylmercaptoacetophenone, having the formula



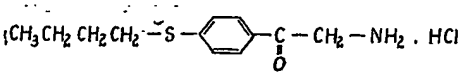
This compound was recrystallized from petroleum ether, thus yielding large colourless crystals when melted at approximately 63° C. 60 g. of alpha-bromo-4-n-butylmercaptoacetophenone dissolved in 300 ml. of acetonitrile was treated with 30 g. of hexamethylenetetramine, thereby producing 88 g. of alpha-bromo-4-n-butylmercaptoacetophenone - hexamethylenetetramine adduct, having the formula



which melted at approximately 113° C. with decomposition.

A mixture of 86 g. of alpha-bromo-4-n-butylmercaptoacetophenone - hexamethylenetetraamine adduct, 85 ml. of concentrated hydrochloric acid, and 170 ml. of ethanol was stirred for about ten hours. The ammonium chloride which separated from the mixture as a white solid was removed by filtration and discarded. The filtrate, after partial evaporation at room temperature under reduced pressure, yielded 13.5 g. of a pale yellowish solid which melted at 140-145° C. (dec.). The filtrate from collection of this solid was reduced in volume by evaporation and a further yield of 35 g. of the product was obtained as a brown gummy solid. This gummy solid was suspended in 50 ml. of acetone, the solution was cooled in an ice-methanol bath, the solid which separated from the cooled solution was collected on a filter and washed several times with cold acetone. There was thus obtained 26.5 g. of a yellowish-tan solid which melted at 140-145° C. (dec.). The two crops of product melting at 140-145° C. were combined and the 40 g. of product was recrystallized from 100 ml. of water containing 3 ml. of concentrated hydrochloric acid. There was thus obtained 32.5 g. of alpha-amino-4-n-butyl-

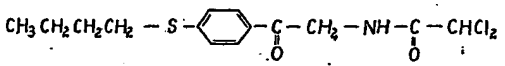
mercaptoacetophenone hydrochloride having the formula



in the form of white flaky crystals. A sample of this product was recrystallized from ethanol and then again from water acidulated with hydrochloric acid to yield the pure compound which melted at 175.5-179.3° C. (dec.).

B. ALPHA - DICHLOROACETYLAMINO - 4 - N-BUTYLMERCAPTOACETOPHENONE

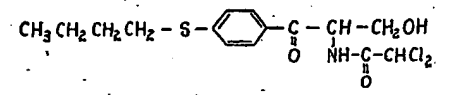
A mixture of 27 g. of dry alpha-amino-4-n-butylmercaptoacetophenone hydrochloride, 125 ml. of anhydrous benzene, and 15 ml. of dichloroacetyl chloride was stirred and heated for fifteen minutes on a steam bath. The reaction mixture was then cooled and the solid which separated from solution was collected on a filter. There was thus obtained 31.6 g. of alpha - dichloroacetylamino - 4 - n - butylmercaptoacetophenone having the formula



Recrystallization of this product from benzene yielded fluffy white needles which melted at 127.4-128° C. with sintering at 120.2° C.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - N - BUTYLMERCAPTOPROPIOPHENONE.

A mixture of 47.5 g. of alpha-dichloroacetylamino-4-n-butylmercaptoacetophenone, 300 ml. of ethanol, and 2 g. of sodium bicarbonate dissolved in 23 ml. of formalin (37% aqueous solution of formaldehyde) was heated at 40-45° C. for four hours. The slurry was cooled to 10° C., filtered, and the solid residue was washed with 40 ml. of methanol and dried. There was thus obtained 41 g. of alpha - dichloroacetylamino - beta - hydroxy-4 - n - butylmercaptopropiophenone having the formula

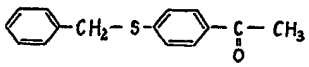


which when recrystallized from benzene in the form of small white crystals, melted at 123.0-123.8° C.

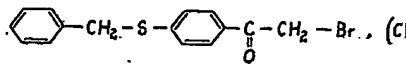
EXAMPLE 6

A. ALPHA -AMINO - 4 - BENZYLMERCAPTOACETOPHENONE HYDROCHLORIDE

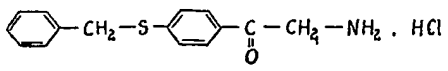
340 g. of benzyl phenyl sulphide was dissolved in 1200 ml. of anhydrous chloroform and 120 ml of acetyl chloride was added to the solution. The resulting mixture was cooled to −10° C. and 226 g. of aluminium chloride was added portionwise at such at rate that the temperature of the reaction mixture did not exceed 0° C. After the addition of the aluminium chloride was completed, the mixture was stirred and allowed to warm to 21° C. The mixture was then poured into ice water. The red chloroform layer was separated from the aqueous layer, washed with 300 ml. of dilute hydrochloric acid, and dried over anhydrous calcium sulphate. The chloroform was then evaporated from the chloroform solution. There was thus obtained as a residue 402 g. of a dark red oil. This oil was dissolved in 1200 ml. of petroleum ether and the resulting solution was filtered hot with charcoal. The yellow filtrate was cooled in an ice bath. 154 g. of yellow solid separated from the cooled solution. This product was recrystallized twice from ethanol and once from petroleum ether. There was thus obtained, in the form of fine white needles which melted at 113.9-115.3° C., 4-benzylmercaptoacetophenone, having the formula



95 g. of 4-benzylmercaptoacetophenone was dissolved in one litre of chloroform and was treated with 62.5 g. of bromine by a procedure similar to the bromination described above in Example 1A. To the solution of alpha-bromo-4-benzylmercaptoacetophenone thus obtained there was added 56 g. of hexamethylenetetramine and the mixture was stirred for two hours. The pinkish-white solid which separated was collected on a filter and washed with 200 ml. of chloroform. The resulting crude alpha-bromo - 4 - benzylmercaptoacetophenone-hexamethylenetetramine adduct, having the formula



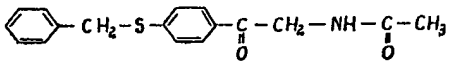
was hydrolyzed directly by stirring it for about ten hours at room temperature (about 25° C.) with 180 ml. of concentrated hydrochloride and 360 ml. of ethanol. The reaction mixture was then cooled to 10° C. The solid was collected on a filter and dried. There was thus obtained 145 g. of crude reaction product. Ammonium chloride was removed from this product by slurrying it with 400 ml. of hot water for ten minutes and then cooling the solution to 10° C. 67 g. of solid separated from the cooled solution. This product was further purified by recrystallization from water containing a little hydrochloric acid. There was thus obtained alpha-amino-4-benzylmercaptoacetophenone hydrochloride, having the formula



in the form of white leaflets which melted at 214.5-216.5° C. (dec.).

B. ALPHA - ACETYLAMINO - 4 - BENZYLMERCAPTOACETOPHENONE

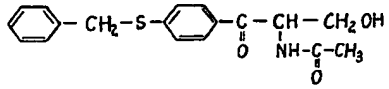
To a slurry of 52 g. of alpha-amino-4-benzylmercaptoacetophenone hydrochloride, 250 ml. of water and 500 g. of ice there was added 40 ml. of acetic anhydride followed by the immediate addition of a solution of 60 g. of sodium acetate trihydrate in 250 ml. of water. The reaction mixture was stirred and allowed to warm to room temperature (about 25° C.), and was then made acid to Congo by addition of hydrochloric acid. The solid was separated from the mixture by filtration, washed with water, and dried. A small sample of this product was purified by recrystallization from acetone. There was thus obtained alpha-acetylamino - 4 - benzylmercaptoacetophenone having the formula



in the form of white needles which melted at 162.6-163.8° C.

C. ALPHA - ACETYLAMINO - BETA - HYDROXY-4 - BENZYLMERCAPTOPROPIOPHENONE

The crude product from step B was slurried and warmed at 40° C. with 3.5 litres of ethanol. To this mixture were added 45 ml. of formalin (37% aqueous solution of formaldehyde) and 4 g. of sodium bicarbonate. Stirring of the reaction mixture at 40° C. was continued for twenty-four hours. The suspended sodium bicarbonate was removed from the solution by filtration and the filtrate was evaporated to a volume of about 100 ml. diluted with water, and the white solid which separated from solution was collected on a filter. There was thus obtained 49 g. of pale yellow solid. This product was recrystallized once from ethylene chloride and once from nitroethane. There was thus obtained alpha-acetylamino - beta - hydroxy - 4 - benzylmercaptopropiophenone, having the formula

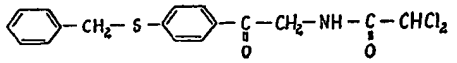


which melted at approximately 161° C.

EXAMPLE 7

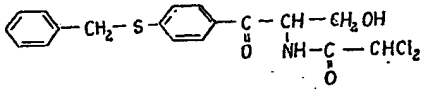
ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - BENZYLMERCAPTOPHENYL-PROPIOPHENONE

12 g. of alpha-amino-4-benzylmercaptoacetophenone hydrochloride (obtained as described above in step A of Example 6), 8 g. of dichloroacetyl chloride, and 500 ml. of dry benzene were refluxed for seven hours. The hot solution was then filtered, 5 g. of solid residue was collected on the filter and the benzene filtrate on cooling yielded an additional 8 g. of the same product, which was alpha - dichloroacetylamino - 4 - benzylmercaptoacetophenone, having the formula



This product, when purified by crystallization, first from ethylene chloride and then from nitroethane, melted at 185.6-186.4° C.

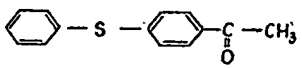
Proceeding in the manner set forth in the above examples, hydroxymethylation of the alpha-dichloroacetylamino - 4 - benzylmercaptoacetophenone by treatment with formaldehyde in the presence of an alkaline condensation catalyst yields alpha-dichloroacetylamino - beta-hydroxy - 4 - benzylmercaptophenylpropiophenone, having the formula



EXAMPLE 8

A. ALPHA - AMINO - 4 - PHENYLMERCAPTOACETOPHENONE HYDROCHLORIDE

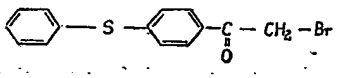
A mixture of 190 g. of diphenyl sulphide, 146 g. of aluminium chloride, and one litre of anhydrous chloroform was stirred and cooled to −5° C. 80 g. of acetyl chloride was added to the mixture slowly, the temperature of the mixture being kept at −5° C. to +5° C. When all of the acetyl chloride had been added, stirring was continued for one hour while the reaction mixture was gradually allowed to warm to room temperature. The mixture was then poured into ice water. The chloroform layer was separated from the mixture and the chloroform was removed from the chloroform solution by distillation under reduced pressure. The residue thus obtained was dissolved in a hot mixture of 150 ml. of benzene and 150 ml. of petroleum ether. When the solution was cooled, 158 g. of 4-phenylmercaptoacetophenone, having the formula



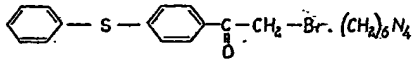
separated from solution. This product melted at approximately 66° C.

A solution of 53 g. of 4-phenylmercaptoacetophenone in 500 ml. of chloroform was treated with 36 g. of bromine at room tem-

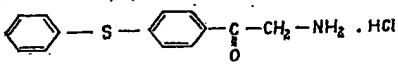
perature. After the bromination was completed, and excess hydrogen bromide was removed from the reaction mixture, a sufficient quantity of 5% aqueous sodium bicarbonate solution was added to render the mixture alkaline to litmus. The chloroform layer was separated and distilled under reduced pressure to remove the chloroform. There was thus obtained as an oil, 69 g. of crude alpha-bromo-4-phenylmercaptoacetophenone, having the formula



The 69 g. of oil was dissolved in 400 ml. of acetonitrile and 32.6 g. of hexamethylenetetramine was added to the solution. The mixture was stirred for thirty minutes and the white creamy solid was then collected on a filter. There was thus obtained 100 g. of crude alpha-bromo - 4 - phenylmercaptoacetophenone-hexamethylenetetramine adduct, having the formula



which melted with decomposition at approximately 206° C. This product was stirred and heated on a steam bath for fifteen minutes with 250 ml. of ethanol and 120 ml. of concentrated hydrochloric acid. The ammonium chloride which separated from the mixture was removed by filtration and the filtrate was allowed to stand for several hours at room temperature. The white solid which separated from the solution was collected on a filter, dissolved in hot anhydrous ethanol, filtered hot with charcoal, and the filtrate was cooled. There separated from the cooled solution 22 g. of alpha - amino - 4 - phenylmercaptoacetophenone hydrochloride, having the formula



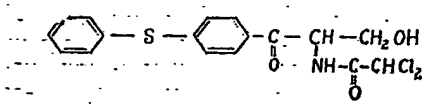
which melted at 216.7-217.0° C. (dec.).

B. ALPHA - DICHLOROACETYLAMINO - 4-PHENYLMERCAPTOACETOPHENONE

A mixture of 22 g. of alpha-amino-4-phenylmercaptoacetophenone hydrochloride, 37 g. of dichloroacetyl chloride and 150 ml. of dry benzene was heated under reflux for thirty minutes. The hot reaction mixture was then filtered. 12 g. of alpha-dichloroacetylamino-4-phenylmercaptoacetophenone separated from the filtrate on cooling. This product melted at 138.5-139.7° C.

C. ALPHA - DICHLOROACETYLAMINO - BETA-HYDROXY - 4 - PHENYLMERCAPTOPROPIOPHENONE

A mixture of 17 g. of alpha-dichloroacetylamino-4-phenylmercaptoacetophenone, 125 ml. of ethanol, 10 ml. of formalin (37% aqueous solution of formaldehyde), and 1 g. of sodium bicarbonate was stirred and heated at 40° C. for one hour and then allowed to stand for several hours at room temperature (about 25° C.). The reaction mixture was then reheated to 40° C., filtered to remove sodium bicarbonate, and the filtrate cooled. 11 g. of solid separated from the cooled filtrate. This product was recrystallized from ethylene chloride, thereby yielding 10.5 g. of pure alpha-dichloroacetylamino - beta - hydroxy - 4-phenylmercaptoacetophenone, having the formula



which melted at 128.5-129.5° C.

Proceeding in accordance with the teachings of the above examples, there can be prepared the following compounds:

alpha - iodoacetylamino - beta - hydroxy - 4-(*p*-tolylmercapto)propriophenone by hydroxymethylating alpha - iodoacetylamino - 4-(*p*-tolylmercapto)-acetophenone.

alpha - (beta - chloropropionylamino)-beta - hydroxy - 4 - cyclohexylmercaptopropiophenone by hydroxymethylating alpha-(beta - chloropropionylamino) - 4 - cyclohexylmercaptoacetophenone;

alpha - acetylamino - beta - hydroxy - 4-methallylmercaptopropiophenone by hydroxymethylating alpha - acetylamino - 4 - methallylmercaptoacetophenone;

alpha - (alpha, beta - dichloropropionylamino) - beta - hydroxy - 4 - tert. - butylmercaptopropiophenone by hydroxymethylating alpha - (alpha, beta - dichloropropionylamino) - 4 - tert. - butylmercaptoacetophenone.

What we claim is:—

1. A process for proparing acylamino phenone compounds, which comprises hydroxymethylating a compound of the formula II herein to produce a compound of the formula I herein.

2. A process according to claim 1, in which the compound of formula II is treated with formaldehyde in the presence of a small amount of sodium bicarbonate.

3. A process according to claim 1 or 2, in which R in the formulae is alkyl, e.g. methyl, and Y is haloalkanoylamino, e.g. dichloroacetylamino.

4. The processes for preparing acylamino phenone compounds of the formula I herein, substantially as set forth in the Examples.

5. Acylamino phenone compounds of the formula I herein, whenever prepared by a process according to any one of the preceding claims.

6. An acylamino phenone compound of the formula I herein.

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Acylamino phenone compounds and method for preparing same

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Abstract

The invention comprises a -acylamino-b -hydroxy - 4 - mercaptopropiophenone compounds of the general formula (wherein R represents a hydrocarbon radical of 1-7 carbon atoms and Y an aliphatic carboxylic acylamino radical), and the preparation thereof by hydroxymethylation (e.g. with formaldehyde in the presence of a small amount of sodium bicarbonate) of compounds of the general formula The reaction may be carried out at 0-70 DEG C., preferably 20-50 DEG C., using formaldehyde in the form of a gas, an aqueous or alcoholic solution or paraformaldehyde. The substituents R and Y may be any of those enumerated in Specification 745,900, compounds in which R is alkyl and Y is haloalkanoylamino being preferred. In examples the following compounds are hydroxymethylated by warming a solution or suspension thereof in ethanol with aqueous formaldehyde and sodium bicarbonate: (1) a acetylamino - 4 - methylmercaptoacetophenone; (2) a - dichloracetylamino - 4 - methylmercaptoacetophenone; (3) a - dichloroacetylamino - 4 - ethylmercaptoacetophenone; (4) a dichloroacetylamino - 4 - n - propylmercaptoacetophenone; (5) a - dichloroacetylamino - 4-n - butylmercaptoacetophenone; (6) a - acetylamino - 4 - benzylmercaptoacetophenone; (7) a - dichloroacetylamino - 4 - benzylmercaptoacetophenone; (8) a - dichloroacetylamino - 4-phenylmercaptoacetophenone. Additional starting materials specified are: a -iodoacetylamino4 - p - tolymercaptoacetophenone, a - (b chloropropionylamino) - 4 - cyclohexylmercaptoacetophenone, a - acetylamino - 4 - methallylmercaptoacetophenone and a - (a :b - dichloropropionylamino - 4 - tert. - butylmercaptoacetophenone. a - Acylamino - 4 - hydrocarbonylmercaptoacetophenones of the second general formula above are prepared by the action of an acylating agent (e.g. an acyl halide or anhydride, advantageously in an anhydrous organic solvent or in an alkaline aqueous solution) on the corresponding amines, which in turn are obtained by reacting the appropriate thiophenol ether with acetyl chloride in the presence of aluminium chloride, brominating the resulting 4-hydrocarbonylmercaptoacetophenone in the a -position, and replacing the bromine atom by NH2, e.g. by condensation with hexamethylene tetramine followed by hydrolysis with aqueous alcoholic hydrochloric acid. The preparation of the starting materials for the examples above is described in detail.